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ORIGINAL ARTICLE

NEUROLOGICAL MANIFESTATIONS OF B_{12} DEFICIENCY IN BIDAR DISTRICT

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ABSTRACT: OBJECTIVE: To investigate the etiological factors resulting in Vitamin B_{12} deficiency in patients with sub-acute combined degeneration (SACD) and other neurological manifestation manifestations. **METHODS**: We undertook a prospective study of 50 patients, all clinically suspected to have Vit B_{12} deficiency; they were investigated clinically, hematologically, biochemically and radiologically. **RESULTS**: There was a dominance of males (41of 50) with the majority in the age group of more than 40 years of age. There was no correlation between the socio-economic and dietary status on the one hand and the clinical manifestation on the other. Anti-intrinsic factor antibodies (AIFAB) were positive in 19 of 50 patients (38%) and anti-parietal cell antibodies (APCAB) were positive in 28 of 50(56%) patients. **CONCLUSION**: We conclude that Pernicious anemia is an important cause of various neurological manifestations including s ACD in the Vitamin B12 deficient population in the age group of more than 40 years, irrespective of the socio-economic and dietary status in the Indian subcontinent. It is supported by the presence of AIFAB ro APCAB in this group.

KEYWORDS: Vitamin B_{12} Deficiency, Paraesthesias.

INTRODUCTION: All naturally occurring form of Vitamin B_{12} (Vit B_{12}) arises in micro-organisms. Some dietary sources of Vit B_{12} are dairy products, eggs, the liver and kidney of animals. The daily requirement (RDA) of Vit B_{12} is 2.2mcg whereas according to the national institute of nutrition Hyderabad, it is 1 micrograms/in Indians. [1]In general, Indians are vegetarians and hence have low B_{12} levels.

Deficiency of Vit B_{12} occurs because of poor intake and/or malabsorption of dietary cobalamin. The result is demyelination of spinal cord, white matter of the brain and peripheral neuropathy.

We here in decided to investigate the neurological manifestation of Vit B_{12} deficiency and its neurological manifestations in people of Bidar district.

PATIENTS AND METHODS: The patients were recruited from the indoor and outdoor Departments of BRIMS, Teaching Hospital, Bidar. The total number of patient studied was 50 of which 9 were females.

The selected patients met the following criteria:

1. Symptoms suggestive of anaemia – fatigability, stomatitis and generalised weakness.
2. Symptoms suggestive neurological involvement – paraesthesias and numbness in limbs, difficulty in activities of daily living like writing, buttoning, mixing food, cutting of bread; loss of balance, difficulty in walking; decreased pace of walking feeling of walking on cotton/ sponge; slipping of footwear; lhermitte's symptom; bladder/ bowel disturbances; impotence; increased forgetfulness irritability, frank dementia and mood and behavioural changes.

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A detailed history of each patient was elicited with reference to economic status, income category processional status and diet.

The patients were examined for the following- pallor, icterus, glossy tongue, hyper-pigmentation of knuckles and vitiligo. Detailed neurological examination was carried out of each patient with special attention to sensory examination and gait analysis. The cognitive functions were assessed by mini mental state examination (MMSE).

Once the patients were selected, various hematological parameters including peripheral smear analysis for megaloblasts, macrocytes, hypersegmented neutrophils and RBC indices were carried out. The work up consisted of routine blood biochemistry, protein electrophoresis, lactate dehydrogenase (LDH) (N<200 I.U), thyroid function tests, serology for syphilis and HIV. Serum Vit B_{12} and folic acid were estimated by Chemiluminiscence. Immunoassay. Vit B_{12} deficiency was said to be present when Vit B_{12} and folic acid were below <200pg/ml and <3.00 ng/ml respetively.[2-3]

Age	15-20 years	20-40 years	41-60 years	More than 60 years	Total
No. of patients	5	7	20	18	50

Table1: Age distribution as observed in 50 Patients

Symptom	No. of patients	%
Paraesthesias	40	80
Loss of balance	38	76
Difficulty in walking	26	52
Mental changes	11	22
Lhermitte's symptom	10	20
Impotence	2	4

Table 2: Symptoms observed in the studied patients

Physical finding	No. of patients	%
Knuckle pigmentation	23	46
Pallor	18	36
Icterus	6	12
Vitilligo	2	4

Table 3: Physical findings observed in patients

The patients were subjected to nerve conduction velocities (NCV) by standard techniques. Magnetic resonance imaging (MRI) of spinal cord was done by conventional sequences to rule out compressive or other intrinsic diseases and to look for hyperintensity of posterior and lateral columns in T2 sequences. Pernicious anemia was said to be present when antiparietal cell antibodies [APCAC > 10 Units; sensitivity 82%, Specificity 60-99%] and / or anti-intrinsic factor antibodies [AIFAB > 1.1 units; sensitivity 49.5%; specificity 99.9%] were raised. [4]Schilling test, as is unavailable in out set up and nearby centers, was not carried out.

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Inpatients with Vit B12 values between 200 and 300pg per milliliter and in the presence of normal folic acid level, in lieu of estimation of Homocysteine and methylamalonic acid, ancillary evidences like hypoproliferative anemia characterized by marked macrocytosis, hypersegmentation of neutrophils, pancytopenia, and signs of ineffective erythropoiesis (Such as elevated level LDH and indirect bilirubin) were assessed.

The standard of living index (SLI) was calculated as per the national family health survey – 2 as follows: [5]

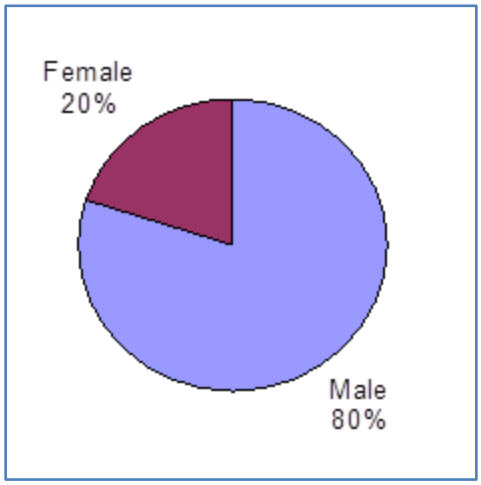
Low SLI – 01-14 Medium SLI-15-24 High SLI- 25-67.

Exclusion criteria in this study were history of diabetes mellitus, alcohol abuse, pancreatitis, gastric or illegal surgery / disease, drug intake like metformin gastric acid suppressants or exposure to Nitric Oxide and malabsorption syndrome and other causes of spinal cord or peripheral nerve disease; other cause of spinal cord or peripheral disease.

Patients with lower motor neuron signs like fasciculations and wasting in the upper limbs were excluded from the study. In the process of selection the following patients were excluded – Cervical myelopathy (7 patients), ataxic neuropathy duo to CIDP with M brand (1 patient), chronic inflammatory demyelinating polyneuropathy (2 patients), GBS with ataxic neuropathy (2 patients), GBS with ataxic neuropathy (2 patients), Tabes dorsalis (1 patient each).

The selected patients met the following criteria; low serum B_{12} levels, laboratory support of megaloblastic anemia, clinical signs of recent cognitive decline and myelopathy- neuropathy.

RESULTS: The so patients predominantly belonged to the middle and elderly age groups (table 1).



Pie Chart 1: Sex distribution in the studied patients

There were 40 males [80%] and 10 females [20%] (Pie chart 1).

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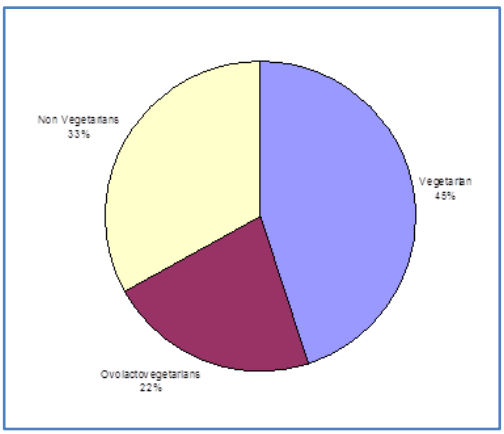

Pie Chart 2: Dietary habits of the studied patients

In the study group, 25 were vegetarians [45%] 10 were ovolactovegetarians [22%] and 15 were non vegetarians [33%] (Pie Chart 2).

Forty patients belonged to the high SLI category [805] and ten belonged to medium SLI [20%].

Of the 50 patients, the commonest symptom was paraesthesias, followed by loss of balance and difficulty in walking (tables 2).

Stomatitis was observed in 29 patients (58%).

The majority had symptoms of less than six months and most below one year of duration.

Disability Score	Gr.0	Gr.1	Gr.2	Gr.3	Gr.4
Mental changes	38	7	3	1	1
Neuropathy	17	11	12	10	0
Pyramidal Tract Dysfunction	34	7	9	0	0
Sensory Changes	14	12	9	5	0
Gait Changes	10	10	21	7	2

Table 4: Disability Score as observed in 50 Patient

Hb (gm%)	No. of patients
Less than 6.5	4
6.5-8	4
8-10	14
10-12	14
More than 12	14

Table 5: Hemoglobin values of 50 patients

Age Group	<40 yrs.	41-60 yrs.	>60 yrs.	Total
High MCV	9	13	14	36 (72%)
High LDH	9	13	12	34 (68%)

Table 6: High MCV 9>93fl) and High LDH (>200 I.U.) as observed in patients

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The most common physical finding was knuckle pigmentation followed by pallor and icterus (Table 3)

Serum B_{12} (pg/ml)	No. of patients
0-50	8
51-100	15
101-150	9
151-200	9
201-250	2
251-300	4
>300	3

Table 7: Range of B_{12} values observed in 50 patients

The neurological disability was calculated as per the disability scoring which is as follows[6]

Parameters	No. of Patients	Age groups (in years)			Dietary Habits		
		20-40	40-60	>60	Veg	Vegans	Non-Veg
AIFAB Positive	4	1	1	2	2	1	1
Both AIFAB and APCAB Positive	15	1	6	8	3	3	9
APCAB Positive	13	0	9	4	4	4	5
AIFAB and APCAB negative	18	9	7	2	13	2	3
Total	**50**		**50**			**50**	

Table 8: Anti-intrinsic Factor Blocking Antibodies (AIFAB) and Anti-Parietal Cell Antibodies (APCAB) as observed in 50

Nerve Conduction Studies	No. of Patients
Sensory Motor Neuropathy	26
Predominantly Motor Neuropathy	3
Pure Sensory Neuropathy	6
Radiculopathy	1
Normal	7
Total	**43**

Table 9: Nerve conduction studies as observed in 43 patients

Disability Score	Gr.0	Gr.1	Gr.2	Gr.3	Gr.4
Mental changes	39	0	0	0	0
Neuropathy	29	8	1	1	0
Pyramidal Tract Dysfunction	26	9	4	0	0
Sensory Changes	5	23	9	2	0
Gait Changes	17	17	4	0	1

Table 10: Follow up Disability Score of 39 Patients

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Gait Disturbances: GR. 0- Normal gait, GR I – Unable to maintain Romberg position. GR 2 – impairment but able to walk unsupported. GR.3 – Support required for walking. GR. 4 – Wheelchair or bedbound.

Sensory Disturbance: GR.0 – No sensory disturbances. GR.1- only in toes and fingers. GR. 2 – in ankle and wrist. GR.3- n upper arms and legs.

Mental Disturbances: GR.0- normal mentation. GR.1 – intellectual impairment but needs no social support. GR.2- Partially dependent for activities of daily living. GR.3- Completely dependent for Activities of Daily Living (ADL).

Neuropathy: GR.0- Absence of neuropathy. GR 1- Loss or reduction of ankle jerk. GR.2- Loss or reduction of reflexes in the arms.

Pyramidal Tract Dysfunction

GR.0 – Absences of pyramidal tract damage. GR. 1- Positive Babinski's sign. GR. 2- Spastic paraparesis GR.3- Spastic Tetraparesis (Table 4).

Hemoglobin values were assessed in 50 patients (Table 5). It was observed that three patients had thrombocytopenia.

High Mean Corpuscular Volume (MCV) was found in 36 patients (72%). The highest MCV was 121.6.on peripheral smear macrocytes were seen in 30 patients (60%). Raised LDH values were observed in 34 patients (68%). The highest LDH was 3488 with hemoglobin of 602gm%. Of the two, MCV is probably slightly more often abnormal then LDH (Table 6).

All the patients had normal values of blood sugar, blood urea, serum creatinine, protein electrophoresis and liver function tests.

Low Vit B_{12} values were noted in 41 patients (82%) and low Vit B_{12} with low folic acid in 7 (14%). There were nine patients in our series that had Vit B_{12} above 200pg /ml – six were between 200 and 300 pg/ml and nine, macrocytosis with hypersegmented neutrophils were seen in six patients and raised LDH (sign. Of ineffective erythropoiesis) in five; the folic acid values in four of nine were normal and low in one. Positive AIFAB and / or APCAD were present in four of these nine and hyperintensities on MRIU spine were observed in another three of the above nine patients (Table 7).

Of the 50 patients AIFAB and APCAB were both elevated in 15 (30%) and AIFAB alone was elevated in 4 (8%) and APCAD alone was elevated 13 patients (26%). Of the remaining 18 patients, 13 were vegetarians, 2 were non vegetarians and 3 were ovolactovegetarians.

Nerve conduction studies were carried out in 40 patients. 26 patients (56%) had evidence of sensory – motor neuropathy (SMN), 3 (6.5%) had changes suggestive of predominantly motor neuropathy, 6 had evidence suggestive of pure sensory neuropathy and only 1 patient had evidence of radiculopathy. 10 patients (23%) showed changed of axonal degeneration and 13 (30%) showed changed of demyelination.

The nerve conduction studies were normal in 7 patients. Although pure motor neuropathy is not a feature of B_{12} deficiency, the occurrence of motor neuropathy observed in the 3 patients is intriguing and inexplicable (Table 9).

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MRI spine was done in 41/50 patients. Of these 26 patients (63%) had hyper-intensities in the posterior columns in T2 sequences, mainly in the cervical region. Follow up MRI of patient no. 2 showed disappearance of hyperintensities after ten month and that of patient no.7 showed decrease of hyperintensities in T2 sequences after 11 months.

After establishing the diagnosis, all the patients were treated with injectable, Vit B_{12}, 1000 micrograms/ day intramuscularly for ten days, and were maintained on monthly injection of the same dose for few months and later on once in 3 to 6 months; oral B complex preparations were simultaneously administered.

39 patients were followed at varying intervals ranging from 2 months to 1 year; even patients were lost to follow up. Most patients showed attenuation of paraesthesias but they persisted with decreasing intensity. Stomatitis disappeared completely in all the patients. Imbalance of gait improved remarkably and early; signs of neuropathy and pyramidal signs gradually disappeared over few months. By the end of one year; most patients, barring sensory symptoms were free of their disability (Table 10).

An elderly lady presented with dementia. After treatment, there was significant improvement in her memory to allow independent activities of daily living.

DISCUSSION: Pernicious anemia is the end stage of an autoimmune disorder in which parietal cell antibodies against H^+K^+- adenosine triphosphates cause loss of gastric parietal cell. The loss of parietal cell initially reduces and then completely prevents production of intrinsic factor. In addition, blocking auto antibodies can bind to the B_{12} binding site for intrinsic factor and prevent the formation of the Vit B_{12} – intrinsic factor complex. Deficiency of intrinsic factor gradually results in Vit B_{12} deficiency.

Vitamin B_{12} is a required coenzyme for 2 important enzymatic reactions. In the first reaction, cobalamin facilitates the methylation of homocysteine by methyltetrahydrofolate into methionine and tetrahydrofolate. Tetrahydrofolate is necessary for normal DNA synthesis of myelin-producing oligodendrocytes. Methionine is subsequently converted to S-adenosyl-methionine (SAM), which is necessary for methylation of myelin sheath phospholipids.

In the second reaction, cobalmin is a coenzyme that converts methylmalonyl coenzyme A into succinyl coenzyme A. Failure of this second reaction to occur results in elevated levels of methylmalonic acid. Excessive methylmalonic acid will prevent normal fatty acid synthesis, or it will be incorporated into fatty acid itself rather than normal malonic acid. If this abnormal fatty acid subsequently is incorporated into myelin or if the methylation of the myelin sheath phospholipids fail to occur, the resulting myelin will be too fragile, and demyelination will occur.[4,6]

The metabolites of Vit B_{12} deficiency, homocysteine and methylmalonic acid, were not tested in the present study as the patients selected had definite manifestations of B_{12} deficiency, both clinically and by other investigatory parameters. Of note, all the patients showed unequivocal improvement by the treatment administered; a therapeutic trial and follow up with clinical improvement of signs and symptoms obviates the need of study these metabolites in Vit B_{12} deficiency.[5] The study of metabolites is indicated when the Vit B_{12} values are in the lower limits of normal (200 to 300 pg /ml) and when the subtle deficiency is a likelihood.[7-8]

Besides studying homocysteine would have escalated the cost while providing no additional benefits.

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In this study, anti-parietal antibodies (APCAB) were elevated in 28 of 50 patients (56%) and anti-intrinsic factor antibodies (AIFAB) were elevated in 19 of 50 patients (38%).

A similar study carried out earlier showed pernicious anemia as the cause of sub-acute combined degeneration in Indians.[9]

Pernicious anemia is the most common cause of Vit B_{12} deficiency in the West. In the West, the APCAD are elevated in90% of patients and AIFAB are positive in 50% patients. [10] It was initially thought that pernicious anemia was restricted to the northern European population. However, subsequent studies have reported the disease in black and Latin-American subjects, with an earlier age of onset in black women.[11]

Pernicious anemia has also been reported among Indians, though rarely: most of the publications describe isolated cases of them.[12-13]

Some Indian workers have also compiled data on Vit B_{12} deficiency and neurological disease.[14, 15] The Vellore group studied 63 cases of Vit B_{12} deficiency. Anti-intrinsic factor antibody was positive in 19(76%) and anti-parietal cell antibody was positive in 17(68%) out of the 25 patients in whom the test was carried out.[12]

Most of the patients in our study presented with paraesthesias, loss of balance and stomatitis over a duration of 3 to 6 months. Some of them had difficulty in walking and one of them presented with frank dementia. Once the diagnosis was established, they were put on Vit B_{12} supplements; most showed significant improvement in their presenting symptoms. Complete disappearance of stomatitis was seen in one after month of treatment. Dementia in one patient improved by nearly 90% after five months of treatment.

We observed male predominance (82%) in our study of 50 patients. This male predominance is puzzling, similar observation has also being made by others.[12]

In our study, 25 were vegetarians, 10 were ovolactovegetarians and 15 were non vegetarians. In most of the previous studies, the majority were vegetarians. All the patients of Jeejebhoy et al[14] and Wadia et al[15] showed that vegetarians predominated the study population. In Wadia and Swami's series, 9 out of 14 patients were vegetarians.[16]

As alluded to, in the West the APCAD are elevated in 90% of patients and AIFAB are positive in 50% of patients.

The cause of Vit B_{12} deficiency and neurological manifestations in our cases appear to be due to age, pernicious anemia, dietary habits and hitherto unknown factors.

In the present study, 20(40%) were from age group 41-60 years, 18(36%) were from age group > 60 years and 12 (24%) were in the age group, 15-40 years. As age advances, the cobalamin level get lowered.

Lindenbaum reported a 12% prevalence of cobalamin deficiency among elderly participants in the Framingham study.17 the low cobalamin level the elderly are attributed to loss of acidity resulting from type B atrophic gastritis; the last may affect 40% of the elderly and is associated with impaired absorption of protein bound Vitamin B_{12}.[18]

The cobalamin levels are low in vegetarians, besides malnutrition is common in India; however most persons are asymptomatic. Indeed, the expatriate as well as Indians at home show cobalamin deficiency.[19,20]

We observed that dietary differences did not influence the clinical presentation. There were 25 vegetarians, 10 ovolacto vegetarian and 15 non-vegetarians. Majority of these patients belonged to

middle-higher middle class of society as per standard living index. Therefore, it appears as through dietary deficiency may not be the sole factor in causing cobalamin deficiency in the middle income group that we studies.

We would like to postulate pernicious anemia as a cause of SACD on the Basis of the following points:

1. Age of onset >40 years in the majority; pernicious anaemia usually does not appear before the age of 30 in adults. The average age at diagnosis is around 60 years.
2. Absence of correlation between the socio-economic and dietary status to the clinical manifestations.
3. In a wide population of Vitamin B_{12} deficient patients, only a small section manifests as SACD; among others pernicious anaemia seems to be one such causative factor.
4. Presence of anti-parietal antibodies and anti-intrinsic factor antibodies.

This is an essentially small observational study; in a large country like India the population is heterogeneous, having diverse dietary habits and hence results of Vit B_{12} deficiency and pernicious anemia are likely to vary among the mixed population groups. Hence such studies need to be carried but in various regions and sector of the country.

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